Remarks

Claims 1-21 are pending. Claims 8-19 are withdrawn. Claims 20-21 are newly added. Support for new claims 20-21 can be found on page 43, lines 16-23 of the specification. The specification was amended to recite SEQ ID NOs to correspond with sequences found in the figures. Also, a description for Figure 41 was added. Basis for the description of Figure 41 can be found throughout the application and in the originally-filed figure itself. The specification was also amended to correct references to color found in the description of the figure and replace it with an accurate figure description. Some of the originally-filed drawings included color. The replacement drawings included with this Amendment were changed to render the drawings in black and white and replace color with symbolic references and to conform the drawings to other requirements of 37 C.F. R. § 1.84. No new matter is believed to be added with these changes.

Sequence Compliance

The Office Action objected to the recitation of sequences in the application without corresponding SEQ ID NOS. The application has been amended to recite SEQ ID NOS at each occurrence of a sequence that falls within the definition of a sequence according to 37 CFR 1.821(a)(1) and (a)(2). Withdrawal of this objection is therefore respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection.

Claims 1-7 were considered to lack adequate written description on the basis that the specification and claims allegedly do not adequately describe the genus comprising regulatable gene expression constructs comprising riboswitches that are activated by a trigger molecule and produce a signal upon activation and which constructs further comprise a control strand, an aptamer domain, and an expression platform domain comprising a regulated strand.

Applicants respectfully traverse, first on the grounds that multiple examples of the genus of riboswitches have been provided, and second on the grounds that the premise of this rejection is not consistent with the law of written description. Regarding the first point, the specification is replete with examples of structural features and sequence relationships of riboswitches. Importantly, the specification provides description of the key structural features and sequence relationships necessary for the operation of riboswitches in general, and provides multiple specific examples of such. For example, the specification (page 105, lines 13-20) states:

> Riboswitches that have been discovered are responsible for sensing metabolites that are critical for fundamental biochemical processes including adenosylcobalamin (AdoCbl) (see Example 1), thiamine pyrophosphate (TPP) (see Example 2), flavin mononucleotide (FMN), S-adenosylmethionine (SAM) (see Example 7), lysine (see Example 5) , guanine (see Example 6), and adenine (see Example 8). Upon interaction with the appropriate small molecule ligand, riboswitch mRNAs undergo a structural reorganization that results in the modulation of genes that they encode.

In each of the examples mentioned above, a detailed description of the riboswitch activated by a trigger molecule is given, along with an explicit discussion of how a trigger molecule interacts with the riboswitch. Thus, Applicants have described the general structure and operation of

riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, and how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules, thus solidifying both the validity of the general description and providing a representative number of examples of the structure of riboswitches. The numerous examples and consensus sequences provided clearly demonstrate Applicants' possession of the broad general subject matter of the present claims. It is hard to imagine how an applicant could provide more descriptive information of a pioneering invention than Applicants have provided.

The Office Action alleges that the specification and claims do not adequately describe the concise structural features (e.g., polynucleotide sequences, structures of all component parts of the gene expression constructs) that distinguish structures within the broadly claimed genus from those without. The Office Action states that the specification teaches the 5'-UTR of the *B. subtilis* xpt-pbuX mRNA as a guanine-responsive riboswitch. The Office Action goes on to state that the specification also teaches a comparison between the 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a conserved RNA motif, termed a "G box" has been identified as a domain for guanine riboswitches. The Office Action then alleges that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required, yet undefined three-dimensional fold necessary for riboswitch function. The Office Action thus implies that a detailed secondary and tertiary structure must be described in the application. This is not the case.

First, Applicants note that riboswitches are made up of different domains that have different roles to play in the operation of the riboswitch. As fully described in the specification,

riboswitches include an aptamer domain and an expression platform. The expression platform of riboswitches generally involves alternative stem structures. The principles of operation and application of platform domains are described in the specification. The formation of hybridized stem structures in RNA is well known in the art, and the examples and principles of the structure and operation of platform domains of riboswitches is described in the specification. The structure-function relationship of the stem structures of platform domains is thoroughly described in the specification and provides all that is required by the written description requirement for this element of the claims.

Aptamer domains are essentially RNA aptamers. RNA aptamers in other contexts have been known and described for many years. The aptamer domains of riboswitches bind to trigger molecules and communicate through the RNA strand to the platform domain. Applicants submit that aptamers can be used and applied in riboswitches based on the description provided in the specification. Applicants discovered that aptamers in riboswitches are modular and can be used and interchanged between riboswitches. As noted in the specification, the aptamer domain of the riboswitch readily adopts the required structure without interference from, and independent of, the other control structures of riboswitches, even in aptamer domains synthesized *in vitro*:

> These conclusions are drawn from the observation that aptamer domains synthesized in vitro bind the appropriate ligand in the absence of the expression platform (see Examples 2, 3 and 6). Moreover, structural probing investigations suggest that the aptamer domain of most riboswitches adopts a particular secondary- and tertiary-structure fold when examined independently, that is essentially identical to the aptamer structure when examined in the context of the entire 5′ leader RNA. This implies that, in many cases, the aptamer domain is a modular unit that folds independently of the expression platform (see Examples 2, 3 and 6).

Specification, page 30, lines 24-30.

Therefore, the generic primary and secondary structural features of riboswitches described in the specification produce the necessary three-dimensional structure, without the need for guidance or further description. This is borne out by Applicants' description and analysis of guanine-responsive riboswitches and their structure. Having identified an example of an aptamer in a guanine-responsive riboswitch (where the aptamer binds to guanine and related compounds), Applicants searched for, found, and identified consensus elements of other guanine aptamers in guanine-responsive riboswitches in other genes (see part C of Figure 41). The conservation and similarity of the primary sequence of aptamers in these riboswitches is strongly indicative that the higher level structure and aptamer function follow from the primary structure. Those of skill in the art would have been able to readily produce such functional riboswitches without concern for the three dimensional structure of the aptamer domain, because the three dimensional structure would have naturally folded into the correct orientation for functionality. Furthermore, as noted in the passage above, the aptamer domain can be a modular component that can be exchanged with other control sequences of the riboswitch. Because the aptamer domain can be exchanged with other control sequences, the riboswitch can comprise any aptamer. The specification comprises multiple examples of such aptamers (see, for example, Figures 11 and 41). Furthermore, aptamers in general are well known in the art and can be produced by known techniques, and are useful with the riboswitches disclosed in the specification.

As mentioned above, the premise of the arguments in the Office Action is not consistent with the law of written description. The mere absence of some specific description in a specification of some embodiment or aspect of a claimed invention does not, by itself, constitute

a lack of adequate written description. Rather, the test is that the applicant conveys with reasonable clarity to those of skill in the art that he or she invented what is claimed. Vas-Cath v. Mahurkar, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). It is clear that every detail of every embodiment is not required. For example, if subject matter is referred to in the specification as being part of the invention, and if that subject matter is not new or unknown subject matter that ordinarily skilled artisans would easily miscomprehend, then such subject matter is adequately described as required by 35 U.S.C. § 112, first paragraph. See Amgen v. Hoechst, 314 F.3d 1313, 1332 (Fed. Cir. 2003). In this case, riboswitches were well described and characterized in the specification, and would not have been easily miscomprehended.

In Amgen, the claims of Amgen's patents referred to types of cells that can be used to produce recombinant human EPO. TKT (Amgen's opponent) argued that, because the Amgen patents did not describe the structure of the claimed cells, the patents failed to provide adequate written description of the claimed subject matter as required by Regents of the University of California v. Eli Lilly, 119 F.3d 1559 (Fed. Cir. 1997) and Enzo Biochem. v. Gen-Probe, 296 F.3d 1316 (Fed. Cir. 2002). The court in Amgen rejected this argument, holding that Amgen's claims, including the recited cells, were adequately described in Amgen's patents. The court noted that unlike in Eli Lilly or Enzo:

> the claim terms at issue here [in Amgen] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend....This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words 'vertebrate' and 'mammalian' readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identify of the members of the genus.'

Amgen at 1332. It is clear from Amgen that there is no absolute requirement for a structural description and no per se requirement for a certain level of structural description. Vertebrate and mammalian cells are highly complicated structures made up of thousands of complicated components. No complete structural description of such cells has ever been made and such cells could not be created independently even if such a description were available. Nevertheless, biologists have had no trouble isolating, culturing and putting such cells to use as exemplified by the invention at issue in Amgen. The court in Amgen recognized that there are reasonable limits to what TKT had argued were absolute requirements of written description established in Eli Lilly.

Applicants have discovered and extensively characterized a new and useful regulatory system of gene expression. Applicants have established the key features of riboswitches and have identified and described the components of riboswitches and noted their relationship to known elements of RNA molecules, such as aptamers and stem-forming regions. This information is sufficient to define the claimed subject matter and to allow those of skill in the art to recognize that Applicants were in possession of riboswitches as claimed. Although the claims may encompass riboswitches having specific structures that are not specifically described in the specification, this is no different than the cells in Amgen. In this regard, and as in Amgen, the present claims make use of known materials in a new combination and used in a new way. The *components* of the claimed riboswitches themselves are not new or unknown materials that those of skill in the art would easily miscomprehend. Further, Applicants have provided a large number of examples showing the breadth and variety of the riboswitch components as well as information on the recognition and application of riboswitches and their components. As a

result, and as in Amgen, the present application satisfies the written description requirement for the present claims. For at least these reasons, the present rejections should be withdrawn.

Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, while being enabling for a method of searching for candidates of the genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule, does not reasonably provide enablement for predictably making and designing the members of the broad genus of molecules claimed.

First, applicants would like to point out that claim 2 appears to be limited to the subject matter which the Examiner has acknowledged as being enabled. Namely, claim 2 is drawn to a specific construct comprising an aptamer domain and an expression platform domain, wherein the aptamer domain and the expression platform domain are heterologous. Furthermore, the Examiner has acknowledged that the subject matter claimed is enabled (page 6, first par.) It is therefore not clear from the rejection which subject matter is not enabled. While the rejection states that searching for candidates of the genus is enabled, it is also stated that predictably making and designing members of the genus is not enabled. However, one of skill in the art

would have easily and readily been able to not only identify the components of the claimed construct, but also to make and design such members. In fact, after the components of the construct are identified, one of ordinary skill in the art could have very easily formed the constructs claimed. The skills needed to make such constructs would have been known to most undergraduate students in a molecular biology lab.

The Office Action contends that the specification does not enable those of skill in the art to predictably make and design the members of the genus of molecules claimed. The Office Action then cites three *Wands* factors in support of this rejection: (1) the state of the prior art and the predictability or unpredictability of the art; (2) the amount of direction or guidance presented in the specification and the presence or absence of working examples; (3) the breadth of the claims and the quantity of experimentation required.

Regarding the state of the art, as the Office Action pointed out, the art teaches various allosteric mechanisms that certain mRNAs use to regulate gene expression in response to various metabolites, including thiamine pyrophosphate and lysine respondent mechanisms that affect thiamine and lysine biosynthetic processes. Therefore, one of skill in the art would have been able to not only create the constructs disclosed in the claims, but also make and use them. The Office Action does not cite any lack in the prior art regarding aptamers and stem-forming RNA (the components of riboswitches) and constructs thereof. Therefore, it appears that the Examiner agrees with the Applicant that there was sufficient knowledge in the art at the time of the invention to allow one of ordinary skill to make and use the claimed invention.

Regarding working examples, the Office Action alleges that the specification lacks a representative number of species of regulatable gene expression constructs comprising nucleic

acid molecules encoding RNA comprising riboswitches operably linked to coding regions (lack of working examples). Applicants point out that the specification contains multiple working examples of the constructs as claimed, as discussed above. The Office Action points to Example 6, which discusses conserved secondary and tertiary structures as a prerequisite for adopting the correct three dimensional structures. The Office Action then alleges that the ability to test various sequences for their ability to cleave target nucleic acid strands in the presence of various ligands, and the postulation of various required, yet undefined higher order structural constraints for riboswitch activities, is not representative of the ability to predictably make and use the broad genus of compounds claimed.

As discussed above, the specification (page 30, lines 24-30) discloses that the aptamer domain of the riboswitch forms a three dimensional structure, and that the aptamer readily adopts the three dimensional structure without interference, even in aptamer domains synthesized *in vitro*:

> These conclusions are drawn from the observation that aptamer domains synthesized in vitro bind the appropriate ligand in the absence of the expression platform (see Examples 2, 3 and 6). Moreover, structural probing investigations suggest that the aptamer domain of most riboswitches adopts a particular secondary- and tertiary-structure fold when examined independently, that is essentially identical to the aptamer structure when examined in the context of the entire 5′ leader RNA. This implies that, in many cases, the aptamer domain is a modular unit that folds independently of the expression platform (see Examples 2, 3 and 6).

Therefore, the generic primary and secondary structural features of riboswitches described in the specification produce the necessary three-dimensional structure, without the need for further guidance. Those of skill in the art would have been able to readily produce such functional riboswitches without concern for the three dimensional structure of such, because the

three dimensional structure would have naturally folded into the correct orientation for functionality. Furthermore, as noted in the passage above, the aptamer domain can be a modular component that can be exchanged with other control sequences of the riboswitch. Because the aptamer domain can be exchanged with other control sequences, the riboswitch can comprise any aptamer. The specification provides numerous examples of aptamers and their components (see, for example, Figures 11 and 41), as well as extensive guidance for their adaptation and use. Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, and how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules, thus solidifying both the validity of the general description and providing a representative number of examples of the structure of riboswitches. The numerous examples and consensus sequences provided clearly provide broad guidance for making and using a wide variety of riboswitches. It is hard to imagine how an applicant could provide more guidance for the production and use of a pioneering invention than Applicants have provided.

Regarding the breadth of the claims and the quantity of experimentation required to practice the invention, the Office Action alleges that the invention as claimed would require the *de novo* determination of sequence and structural characteristics of a broad genus of riboswitches. As discussed above, this is not true. First, the components of riboswitches were types of structures (aptamers and stem-forming RNA) known in the art, so the determination of sequence and structural characteristics would not have been "*de novo*." Second, applicant has provided numerous examples and clear guidance in the specification for making and using the

claimed constructs, so that those of skill in the art could readily produce the claimed construct without the need for undue experimentation.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. At most, the Office Action identifies that some experimentation might be required to make some of the claimed riboswitches. However, this appears to be based merely on the fact that the specification does not contain a literal and complete structural description of every claimed riboswitch. The enablement requirement does not ask for so much. It should be noted that the pending claims are drawn to constructs that could have easily been made by one of skill in the art based upon the disclosure. *See* United States v. Telectronics, Inc., 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 199 USPQ 659 (CCPA 1976). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984).

Initially, the Patent Office must accept the objective truth of statements made in the specification. If such statements are to be called into question, the Patent Office is burdened with providing evidence or convincing argument why those of skill in the art would doubt the statements. *See In re* Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). Applicant need not present counter evidence if the Patent Office fails to meet this burden.

In assessing whether undue experimentation would be required to make and use the claimed constructs, it is important to focus on what would actually have to be done in order to make and use the constructs. The claimed constructs comprise a regulatable gene expression

construct comprising a nucleic acid molecule encoding an RNA comprising a riboswitch operably linked to a coding region, wherein the riboswitch regulates expression of the RNA, wherein the riboswitch and coding region are heterologous. Thus, one wishing to make and use the claimed constructs need only (1) obtain a riboswitch and a coding region and (2) operably link the two.

Applicants submit that practice of none of these steps would require undue experimentation and that the specification supports this conclusion. First, producing an RNA construct was well within the ability of those of skill in the art at the time of the invention and to do so would not have required undue experimentation. Applicant gives multiple examples in the specification of riboswitches that can be used with the claimed invention, and carefully outline the components thereof, and how they can be obtained and used (see, for example, page 35 line 23 through page 43 line 14 of the specification). Applicant gives detailed information regarding the domains of the riboswitch, including both the aptamer and the expression platform. Thus, producing a construct as claimed would not require undue experimentation.

Second, using the constructs was within the ability of those of skill in the art at the time of the invention. Applicants submit that it would not have required undue experimentation for those of skill in the art to use such constructs, as constructs in general and their applications were not only well known in the art at the time of the invention, but clearly discussed in the specification.

For all of the above reasons, applicants submit that the present claims are fully enabled and that the present rejection does not provide persuasive evidence or argument to the contrary. Accordingly, the present rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102

Claims 1-7 were rejected under 35 U.S.C. § 102(a) as being anticipated by Breaker et al. (Curr. Opin. Biotech 13:31-39, Feb. 1, 2002). Applicants respectfully traverse this rejection.

The claims are drawn to a regulatable gene expression construct comprising a nucleic acid molecule encoding an RNA comprising a riboswitch operably linked to a coding region, wherein the riboswitch regulates expression of the RNA, wherein the riboswitch and coding region are heterologous. Breaker et al. does not teach riboswitches at all, but instead teaches intramolecularly cleaving ribozymes. As disclosed in the specification, both an aptamer domain and an expression platform make up a riboswitch, as opposed to a ribozyme. Breaker et al. teaches no such elements and Breaker et al. fails to disclose any regulatable gene expression construct. The instant specification, on the other hand, discloses control elements of the aptamer, such as alternative P1 stems, that regulate RNA expression. This is significantly different than the teachings of Breaker et al. Therefore, applicants respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $60.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(3), and a Request For Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is

hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges — Date: 4/23/2007